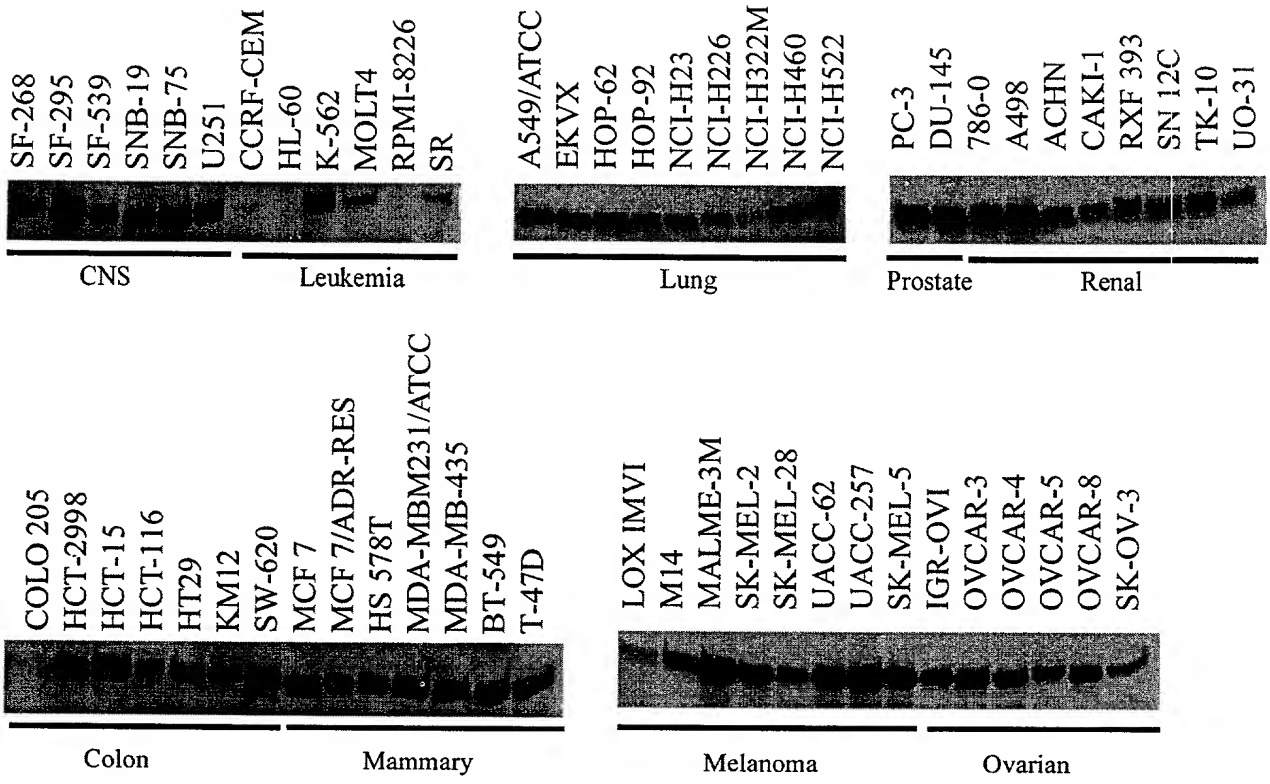
Figure 1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SF-295
SF-539
SNB-19
SNB-75
U251
CCRF-CEM
HL-60
K-562
MOLT4
RPMI-8226
SR
A549/ATCC
EKVX
HOP-62
HOP-92
NCI-H23
NCI-H226
NCI-H322M
NCI-H460
NCI-H522
PC-3
DU-145
786-0
A498
ACHN
CAKI-1
RXF 393
SN 12C
TK-10
UO-31
CNS
Leukemia
Lung
Prostate
Renal
COLO 205
HCT-2998
HCT-15
HCT-116
HT29
KM12
SW-620
MCF 7
MCF 7/ADR-RES
HS 578T
MDA-MBM231/ATCC
MDA-MB-435
BT-549
T-47D
LOX IMVI
M14
MALME-3M
SK-MEL-2
SK-MEL-28
UACC-62
UACC-257
SK-MEL-5
IGR-OVI
OVCAR-3
OVCAR-4
OVCAR-5
OVCAR-8
SK-OV-3
Colon
Mammary
Melanoma
Ovarian

Figure 2

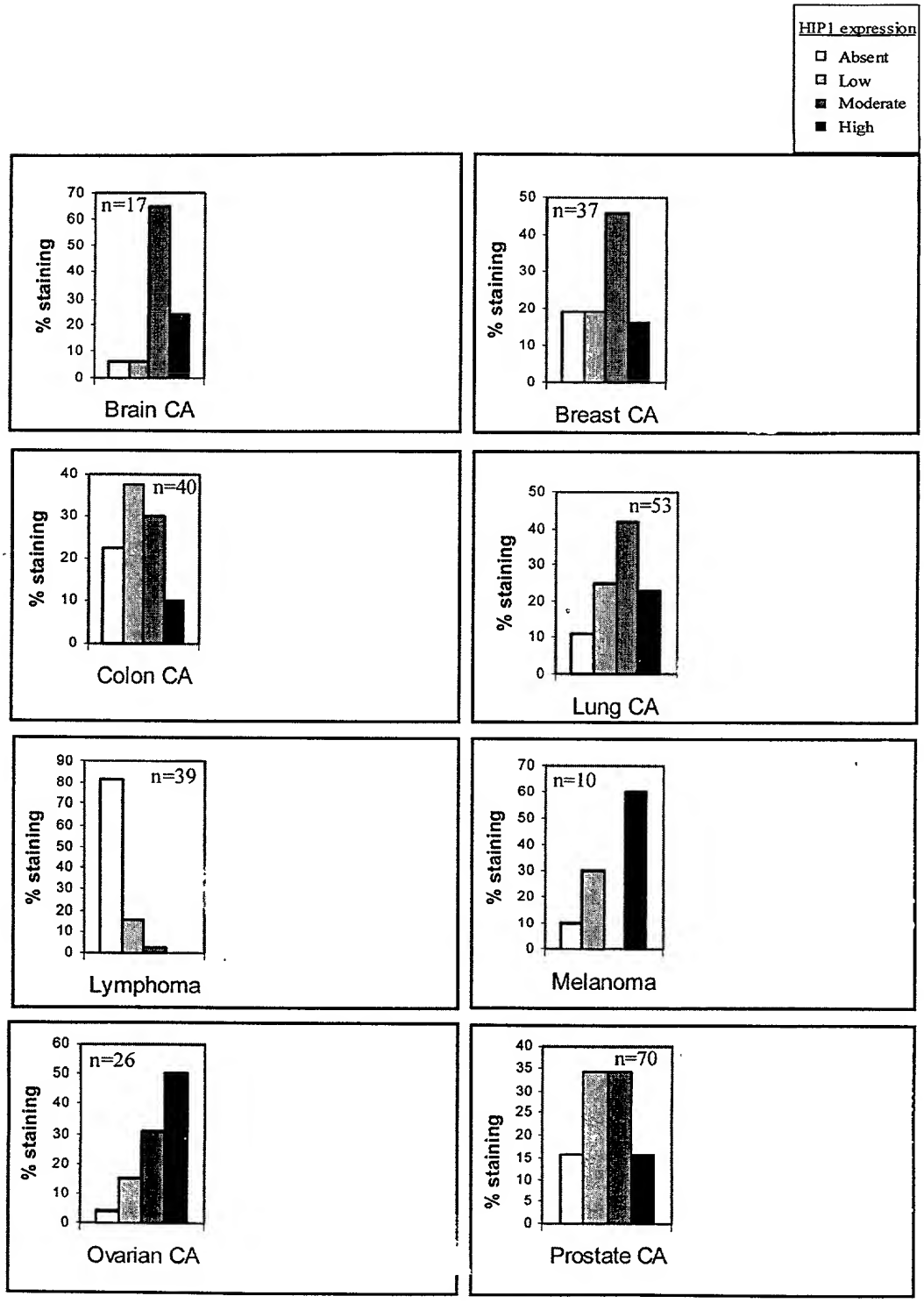
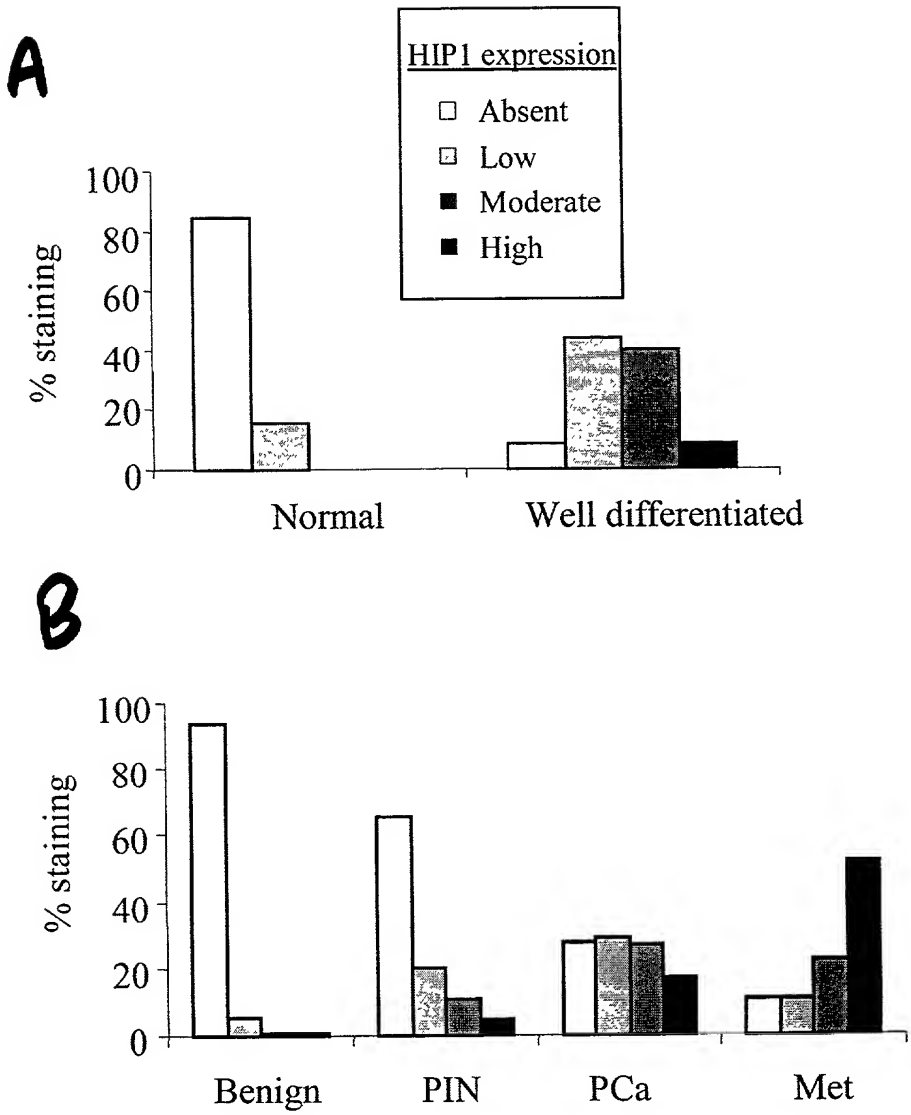

HIP1 expression
Absent
Low
Moderate
High
% staining
n=17
Brain CA
n=37
Breast CA
n=40
Colon CA
n=53
Lung CA
n=39
Lymphoma
n=10
Melanoma
n=26
Ovarian CA
n=70
Prostate CA

Figure 3


A
HIP1 expression
Absent
Low
Moderate
High
% staining
100
80
60
40
20
0
Normal
Well differentiated
B
% staining
100
80
60
40
20
0
Benign
PIN
PCa
Met

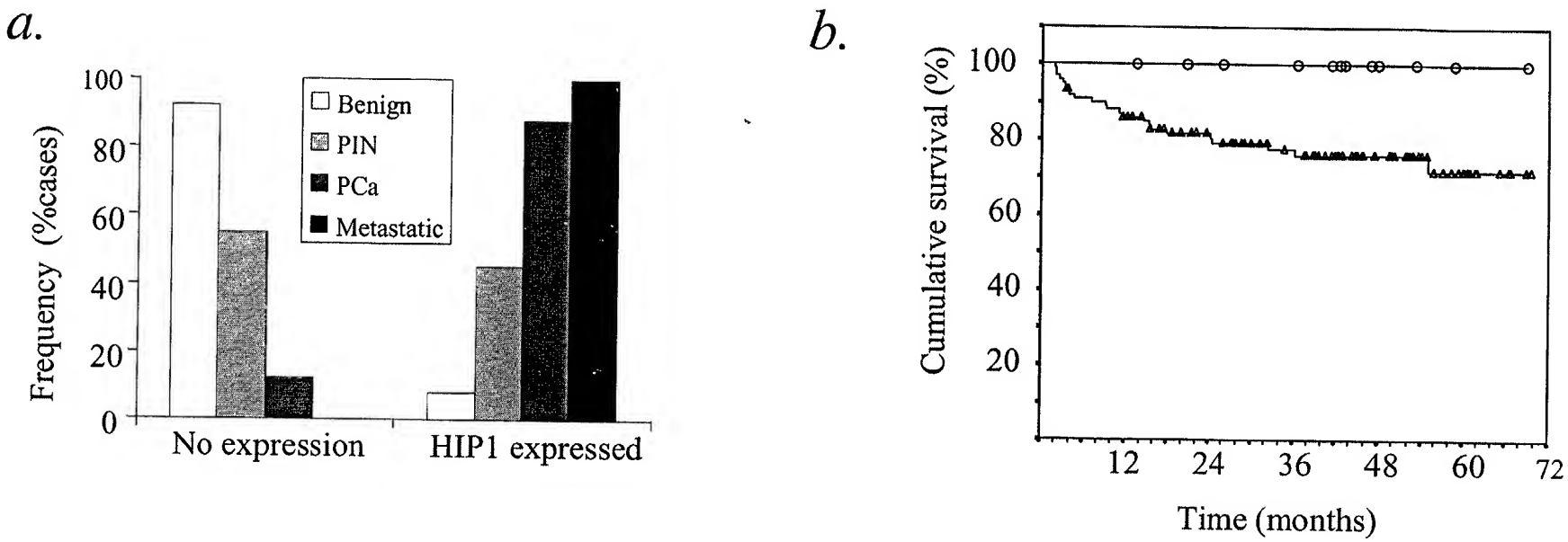

a.
Frequency (%cases)
100
80
60
40
20
0
Benign
PIN
PCa
Metastatic
No expression
HIP1 expressed
b.
Cumulative survival (%)
100
80
60
40
20
12
24
36
48
60
72
Time (months)

Figure 4

Figure 5

		HIP1 expression				Total
		Absent	Low	Moderate	High	
ID #	21	6				6
	22		2			2
	23	1	1	1		3
	25	1	3			4
	26		2	1		3
	31			3	1	4
	32		1	2	1	4
	33				2	2
	38	1		1	4	6
	43		2	2	1	5
	44	2	2			4
	45		2			2
	53		1	2	1	4
	56			2		2
	58			3	1	4
	62	1		1	2	4
	63			5	1	6
	65	1	1	1	2	5
	66	1	1	1		3
	67	2	1		1	4
	70	2	1	2		5
	73		1	6		7
	75	2				2
	76	1	3	1		5
	77	3	1			4
	78	1	2			3
	82	1	2			3
	83	1	1	1	3	6
	84	2	1	1	2	6
	85	1	3	1		5
	89	1	1	3	1	6
	91			4		4
	92	1	1	1		3
	93		1	2	2	5
	96	2	1	1	2	6
	97	1	2	1		4
	99			2	2	4
	101		2	4		6
	102	4			1	5
	103		4			4
	105		2	1		3
	106	1	1		1	3
	108		1	2	3	6
	109		1	5		6
	110	3				3
	111	4	1			5
	113	2		2		4
	114	2				2
	115				2	2
	117			2		2

		HIP1 expression				Total
		Absent	Low	Moderate	High	
ID #	118		1	3		4
	119		2	3	2	7
	123	3	3	1		7
	125	4	2			6
	127	3	1			4
	128			1	3	4
	129	3	1			4
	131	1	1			2
	132			3	1	4
	141			2	2	4
	142	2	3			5
	144	1	3	2	1	7
	145	2				2
	153		1	1		2
	154	2				2
	155				4	4
	159	4	2			6
	161	2				2
	162	1	1	1		3
	164			1	3	4
	165		4	2		6
	169		2			2
	170	3	2	1		6
	171			2		2
	172	2				2
	173	3		1		4
	175	3				3
	177	4	2			6
	178	2	1			3
	179	3	1			4
	180	1			3	4
	181	4				4
	182	2				2
	183		2			2
	186		4			4
	194	4	1			5
	194	2	1			3
	195	1	5	1		7
	199		1	1	1	3
	204		3	1		4
	205			2	2	4
	206		6			6
	207		4			4
	208			3	1	4
	209			2	3	5
	212	1	4	1	3	9
	213	2	3	2		7
	214		1	1	3	5
	217		1	2	3	6
	218	1	6			7

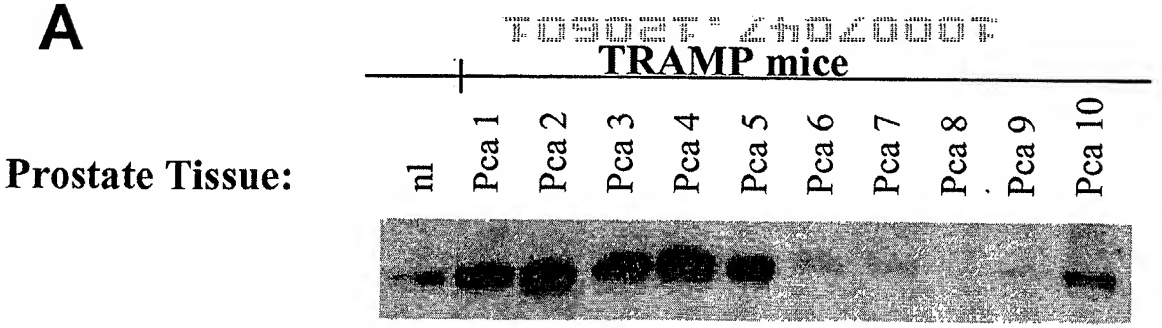
Received: 2/06/2006

		HIP1 expression				Total
		Absent	Low	Moderate	High	
ID #	220		1		5	6
	225		1	3		4
	228			3		3
	229	1		2	1	4
	230	2				2
	231			2	1	3
	234			2		2
	235		3	1		4
	236	2	3			5
	237	4	1			5
	238	2				2
	239		3	2		5
	241	2	1	1		4
	248			2		2
TOTAL		128	136	123	76	463

Exhibit 2 Page 6 of 26

Figure 6

A


TRAMP mice
Prostate Tissue:
nl
Pca 1
Pca 2
Pca 3
Pca 4
Pca 5
Pca 6
Pca 7
Pca 8
Pca 9
Pca 10

B

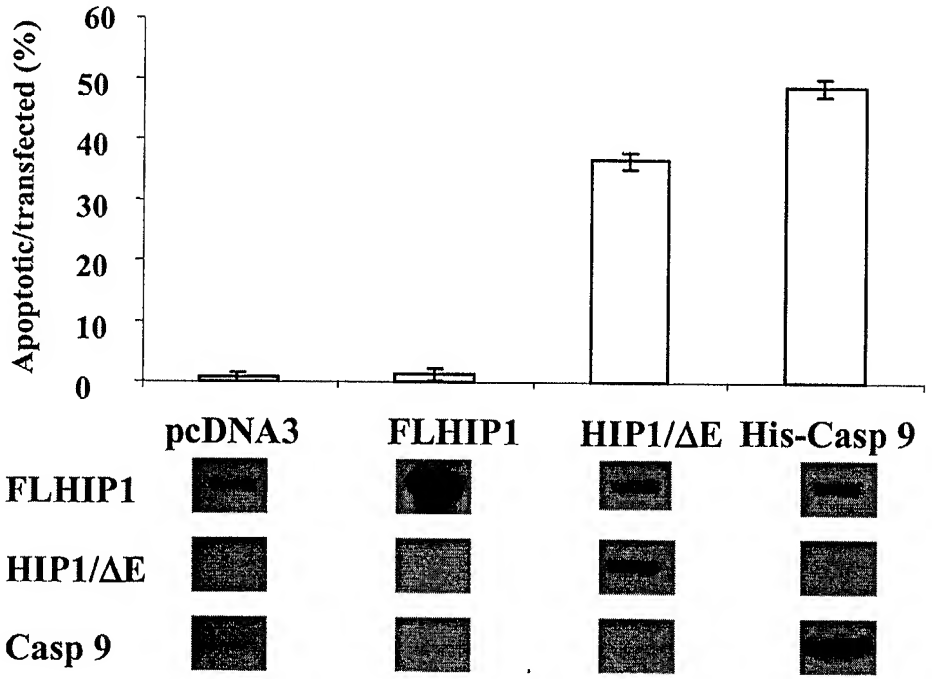

Apoptotic/transfected (%)
60
50
40
30
20
10
0
pcDNA3
FLHIP1
HIP1/ΔE
His-Casp 9
FLHIP1
HIP1/ΔE
Casp 9

Figure 7
Full length HIP1 (SEQ ID NO:1)

ccaagcttggtacccccggggcagccgagggcccctgactcggctcctcgcggcgacatggatcggatggc
cagctccatgaagcaggtgcccaacccactgcccaaggtgctgagccggcgcggggtcggcgctgggctgg
aggcggcggagcgcgagagcttcgagcggactcagactgtcagcatcaataaggccattaatacgcaggaa
gtggctgtaaaggaaaaacacgccagaacgtgcatactgggcacccaccatgagaaaggggcacagacctt
ctggtctgttgtcaaccgcctgcctctgtctagcaacgcagtgctctgctggaagttctgccatgtgttcc
acaaactcctccgagatggacacccgaacgtcctgaaggactctctgagatacagaaatgaattgagtgac
atgagcaggatgtggggctacctgagcgaggggtatggccagctgtgcagcatctacctgaaactgctaag
aaccaagatggagtaccacaccaaaaatcccaggttcccaggcaacctgcagatgagtgaccgccagctgg
acgaggctggagaaagtgacgtgaacaacttttcccagttaacagtggagatgtttgactacctggagtgt
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gcagtgccgcctcgccccgctgatccaggtcatcttggactgcagccacctttatgactacactgtcaagc
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gcctctcagcagaatttatttgacaacaagtttgatgacatctttggcagttcattcagcagtgatcccctt
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ggccccccaactgtggtagctccagcgatggtgctgcccaggcctctcggtgctccatctccgcctccaca
ctgaccaagtgctggcccacccagtccatgctccagggtcaggcggagctgctgagtgacagctttcctca
aaaagcagaaggagagtgagtgcctttccctcctaaagctgaatcccggcggaaagcctctgtccgccttt

PATENT - PENDING

acaagggagaagacaacagaaagagggacaagagggttcacacagcccagttcccgtgacgaggctcaaaa
acttgatcacatgcttgaatggagctggtgagatcaacaacactacttccctgccggaatgaactgtccgt
gaatggtctctgtcaagcgggccgtctcccttggcccagagacggagtgtgggagtgattcccaactcctt
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tcaagcacttcggaattcctgcagcccgggcggccgctcgagcatgcnntagagggcccta

PLEASE CANCEL

Figure 8
Full length HIP1 (SEQ ID NO:2)

MDRMASSMKQVPNPLPKVLSRRGVGAGLEAAERESFERTQTVSINKAINTQEVAVKEKHARTCILGTHHEK
GAQTFWSVVNRLPLSSNAVLCWKFCHVFHKLLRDGHPNVLKDSLRYRNELSDMSRMWGYLSEGYGQLCSIY
LKLLRTKMEYHTKNPRFPGNLQMSDRQLDEAGESDVNNFSQLTVEMFDYLECELNLFQTVFNSLDMSRSVS
VTAAGQCRLAPLIQVILDCSHLYDYTVKLLFKLHSCLPADTLQGHRDRFMEQFTKLKDLFYRSSNLQYFKR
LIQIPQLPENPPNFLRASALSEHISPVVVIPAEASSPDSEPVLEKDDLMDMDASQQNLFDNKFDDIFGSSF
SSDPFNFNSQNGVNKDEKDHLIERLYREISGLKAQLENMKTESQRVVLQLKGHVSELEADLAEQQHLRQQA
ADDCEFLRAELDELRRQREDTEKAQRSLSEIERKAQANEQRYSKLKEKYSELVQNHADLLRKNAEVTKQVS
MARQAQVDLEREKKELEDSLERISDQGQRKTQEQLEVLESLKQELATSQRELQVLQGSLETSAQSEANWAA
EFAELEKERDSLVSGAAHREEELSALRKELQDTQLKLASTEESMCQLAKDQRKMLLVGSRKAAEQVIQDAL
NQLEEPPLISCAGSADHLLSTVTSISSCIEQLEKSWSQYLACPEDISGLLHSITLLAHLTSDAIAHGATTC
LRAPPEPADSLTEACKQYGRETLAYLASLEEEGSLENADSTAMRNCLSKIKAIGEELLPRGLDIKQEELGD
LVDKEMAATSAAIETATARIEEMLSKSRAGDTGVKLEVNERILGCCTSLMQAIQVLIVASKDLQREIVESG
RGTASPKEFYAKNSRWTEGLISASKAVGWGATVMVDAADLVVQGRGKFEELMVCSHEIAASTAQLVAASKV
KADKDSPNLAQLQQASRGVNQATAGVVASTISGKSQIEETDNMDFSSMTLTQIKRQEMDSQVRVLELENEL
QKERQKLGELRKKHYELAGVAEGWEEGTEASPPTLQEVVTEKE*SQTNTPYVSVNPCYLSRVCYFPSHRPN
PWSPRGSHTTAITQCRGHA*HFQRLPP*RHPFCLDPWISTASYGGWLGFLVLFFFFKFHSHSQLSQRAHPW
G*VSRAPQLW*LQRWCCPGLSVLHLRLHTDQVLAHPVHAPGSGGAAE*QLSSKSRRRVSAFPS*S*IPAES
LCPPLQGRRQQKEGQEGSHSPVPVTRLKNLITCLNGAGEINNTTSLPE*TVREWSLSSGPSPLAQRRSVGV
IPNSFLQTSALASS*IGRSFHLLRN*QTRKIRCNCSHQGRTLYLVCYP*YLLLTSLKQQQPTKRCLEQSEL
QV*L*QSSSFCPATSAFKNQKKGQGAGLLLTWIPKQGDHLELLGQRK*ERTEPAAPTPFSHMPQALAALWT
G*GQRAHEQLARDGQPNSTFPLLDGPQHLSDLLILGKQRLPSLSIATHWW*PSSTSEFLQPGRPLEHAXEG
P

(* are stop sequences)

Figure 9
Delta ENTH (SEQ ID NO:3)

gttaacagtggagatgtttgactacctggagtgtgaactcaacctcttccaaacagtattcaactccctgg
acatgtcccgctctgtgtccgtgacggcagcagggcagtgccgcctcgccccgctgatccaggtcatcttg
gactgcagccacctttatgactacactgtcaagcttctcttcaaactccactcctgcctcccagctgacac
cctgcaaggccaccgggaccgcttcatggagcagtttacaaagttgaaagatctgttctaccgctccagca
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caacactacttccctgccggaatgaactgtccgtgaatggtctctgtcaagcgggccgtctcccttggccc
agagacggagtgtgggagtgattcccaactcctttctgcagacgtctgccttggcatcctcttgaatagga
agatcgttccaccttctacgcaattgacaaacccggaagatcagatgcaattgctcccatcagggaagaac
cctatacttggtttgctacccttagtatttattactaacctcccttaagcagcaacagcctacaaagagat
gcttggagcaatcagaacttcaggtgtgactctagcaaagctcatctttctgcccggctacatcagccttc

Replacement Sheet

aagaatcagaagaaaggccaaggtgctggactgttactgacttggatcccaaagcaaggagatcatttgga
gctcttgggtcagagaaaatgagaaaggacagagccagcggctccaactcctttcagccacatgccccagg
ctctcgctgccctgtggacaggatgaggacagagggcacatgaacagcttgccagggatgggcagcccaac
agcacttttcctcttctagatggaccccagcatttaagtgaccttctgatcttgggaaaacagcgtcttcc
ttctttatctatagcaactcattggtggtagccatcaagcacttcggaattcctgcagcccgggcggccgc
tcgagc

Application Serial No. 10/809,055

Figure 10
Delta ENTH (SEQ ID NO:4)

MFDYLECELNLFQTVFNSLDMSRSVSVTAAGQCRLAPLIQVILDCSHLYDYTVKLLFKLHSCLPADTLQGH
RDRFMEQFTKLKDLFYRSSNLQYFKRLIQIPQLPENPPNFLRASALSEHISPVVVIPAEASSPDSEPVLEK
DDLMDMDASQQNLFDNKFDDIFGSSFSSDPFNFNSQNGVNKDEKDHLIERLYREISGLKAQLENMKTESQR
VVLQLKGHVSELEADLAEQQHLRQQAADDCEFLRAELDELRRQREDTEKAQRSLSEIERKAQANEQRYSKL
KEKYSELVQNHADLLRKNAEVTKQVSMARQAQVDLEREKKELEDSLERISDQGQRKTQEQLEVLESLKQEL
ATSQRELQVLQGSLETSAQSEANWAAEFAELEKERDSLVSGAAHREEELSALRKELQDTQLKLASTEESMC
QLAKDQRKMLLVGSRKAAEQVIQDALNQLEEPPLISCAGSADHLLSTVTSISSCIEQLEKSWSQYLACPED
ISGLLHSITLLAHLTSDAIAHGATTCLRAPPEPADSLTEACKQYGRETLAYLASLEEEGSLENADSTAMRN
CLSKIKAIGEELLPRGLDIKQEELGDLVDKEMAATSAAIETATARIEEMLSKSRAGDTGVKLEVNERILGC
CTSLMQAIQVLIVASKDLQREIVESGRGTASPKEFYAKNSRWTEGLISASKAVGWGATVMVDAADLVVQGR
GKFEELMVCSHEIAASTAQLVAASKVKADKDSPNLAQLQQASRGVNQATAGVVASTISGKSQIEETDNMDF
SSMTLTQIKRQEMDSQVRVLELENELQKERQKLGELRKKHYELAGVAEGWEEGTEASPPTLQEVVTEKE*S
QTNTPYVSVNPCYLSRVCYFPSHRPNPWSPRGSHTTAITQCRGHA*HFQRLPP*RHPFCLDPWISTASYGG
WLGFLVLFFFFKFHSHSQLSQRAHPWG*VSRAPQLW*LQRWCCPGLSVLHLRLHTDQVLAHPVHAPGSGGA
AE*QLSSKSRRRVSAFPS*S*IPAESLCPPLQGRRQQKEGQEGSHSPVPVTRLKNLITCLNGAGEINNTTS
LPE*TVREWSLSSGPSPLAQRRSVGVIPNSFLQTSALASS*IGRSFHLLRN*QTRKIRCNCSHQGRTLYLV
CYP*YLLLTSLKQQQPTKRCLEQSELQV*L*QSSSFCPATSAFKNQKKGQGAGLLLTWIPKQGDHLELLGQ
RK*ERTEPAAPTPFSHMPQALAALWTG*GQRAHEQLARDGQPNSTFPLLDGPQHLSDLLILGKQRLPSLSI
ATHWW*PSSTSEFLQPGRPLEH

(* are stop sequences)

Replacement Sheet

Figure 11

Domain Structure of HIP1

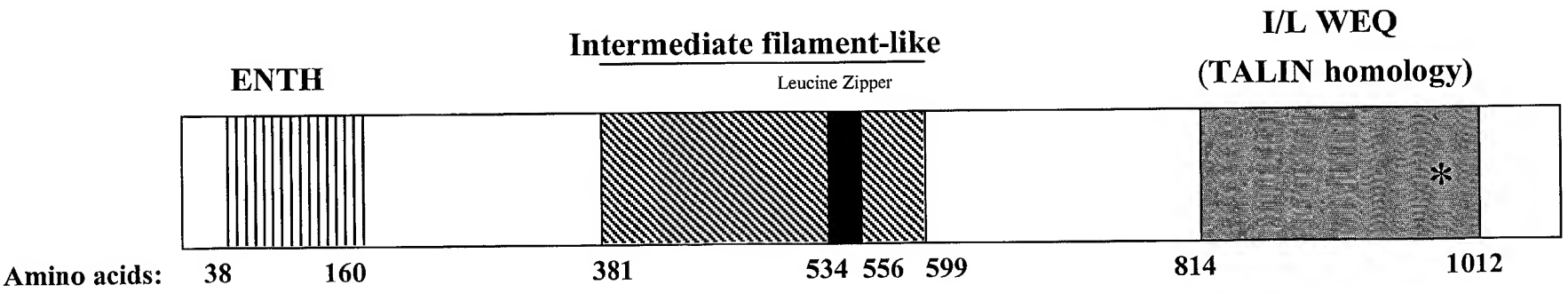
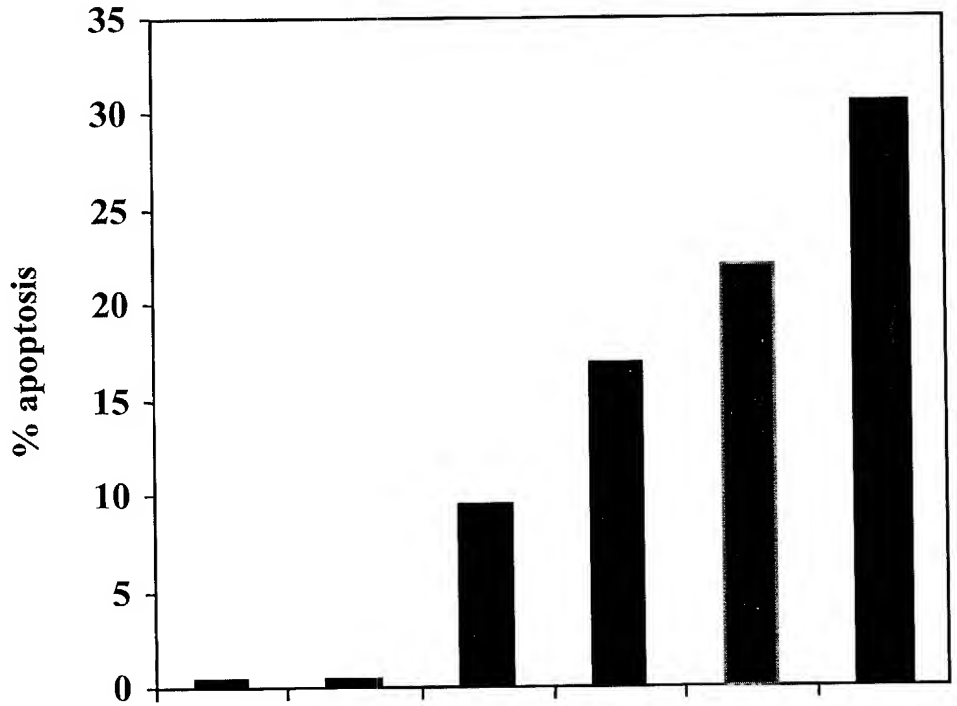


Figure 12

Rescue of apoptosis caused by ΔE with FLHIP1



pcDNA3	1.5	1	0.5	0	0.5	1
FLHIP1	0.5	1	1	1	0.5	0
HIP1/ΔE	0	0	0.5	1	1	1
β-gal	1	1	1	1	1	1

18 h post-transfection

Figure 13

Rescue only with Akt/Dncasp9

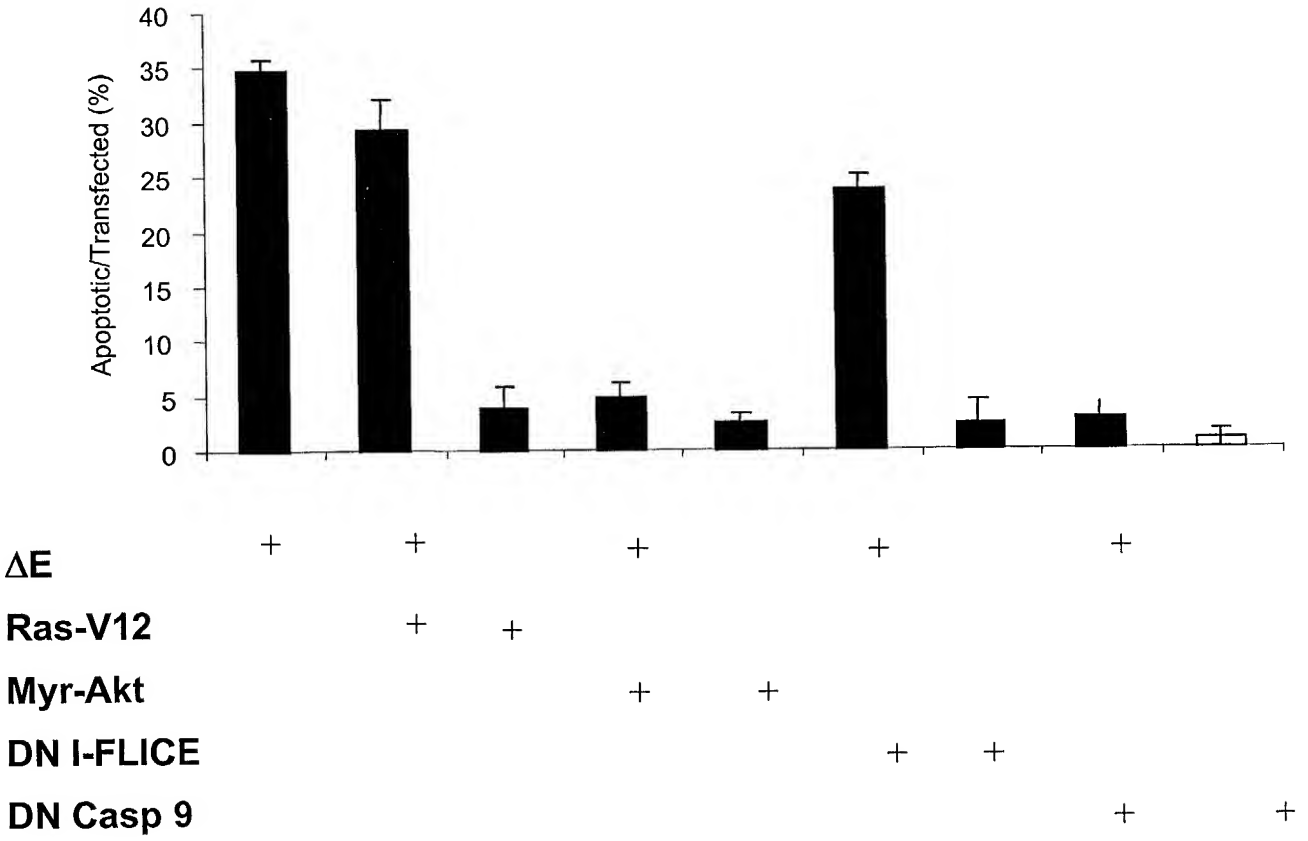


Figure 14

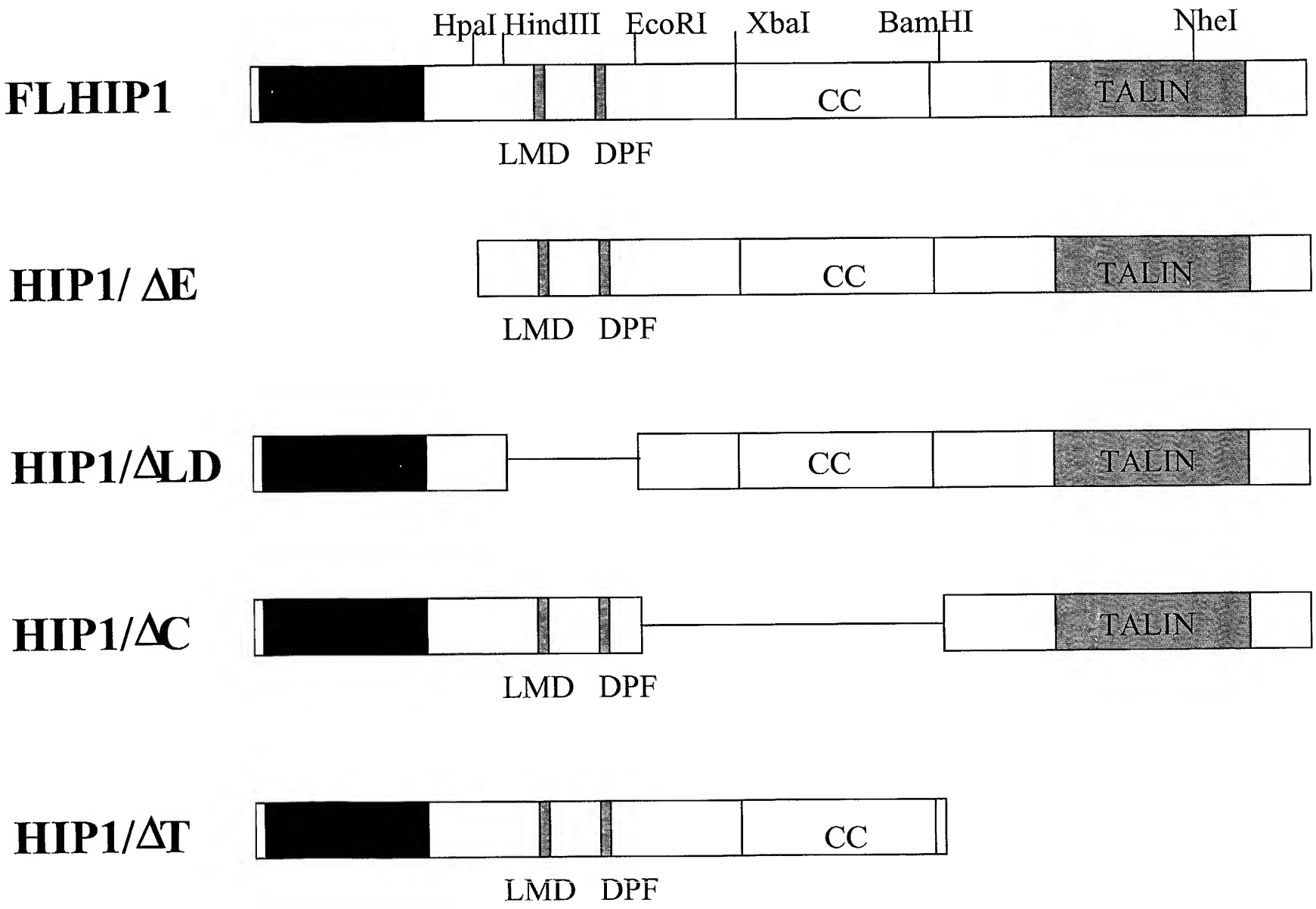

HpaI
HindIII
EcoRI
XbaI
BamHI
NheI
FLHIP1
CC
TALIN
LMD
DPF
HIP1/ ΔE
CC
TALIN
LMD
DPF
HIP1/ΔLD
CC
TALIN
HIP1/ΔC
TALIN
LMD
DPF
HIP1/ΔT
CC
LMD
DPF

Figure 15

Vector Construction Strategy for HIP1/PDGFβR knock-in

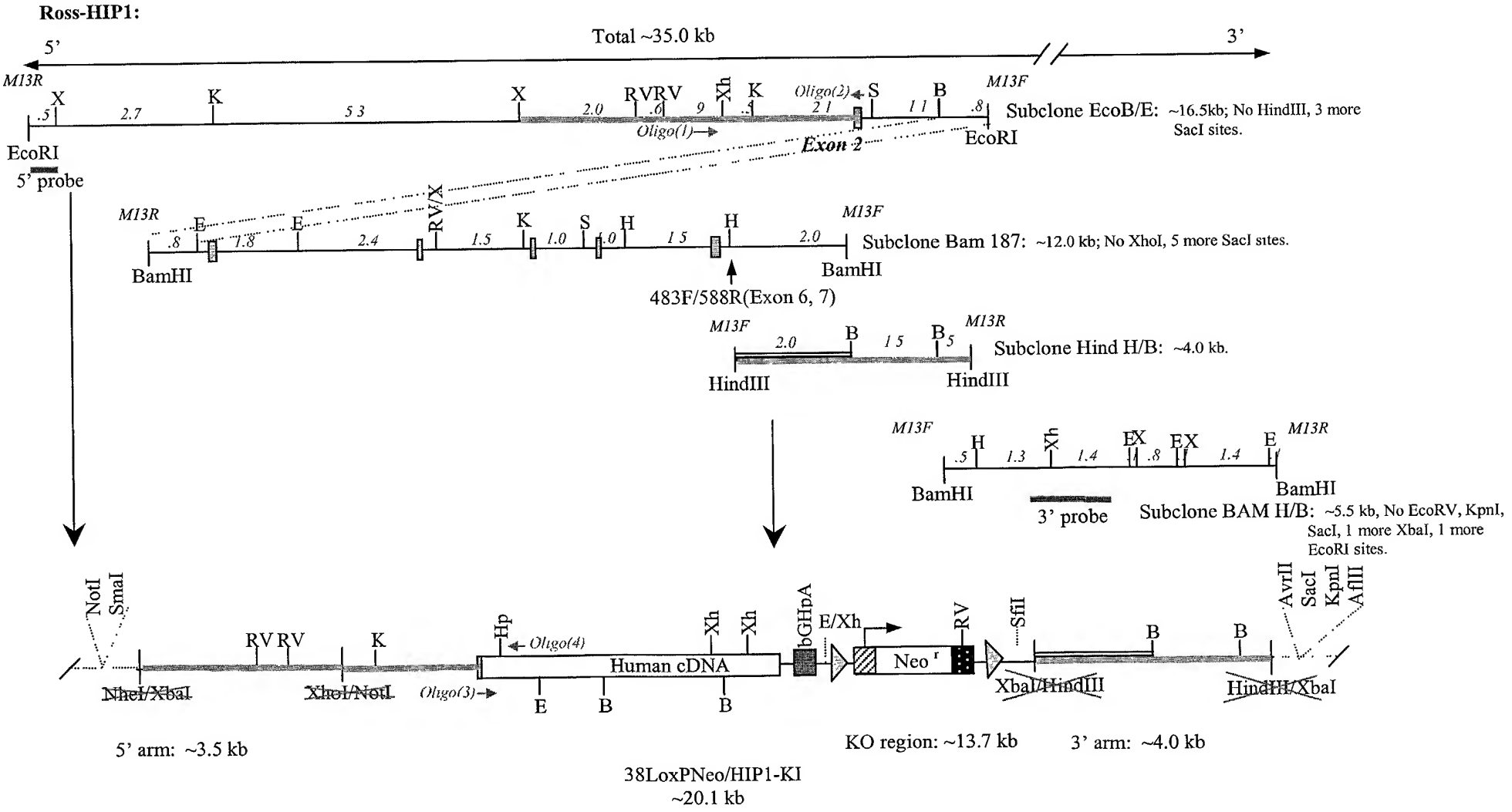
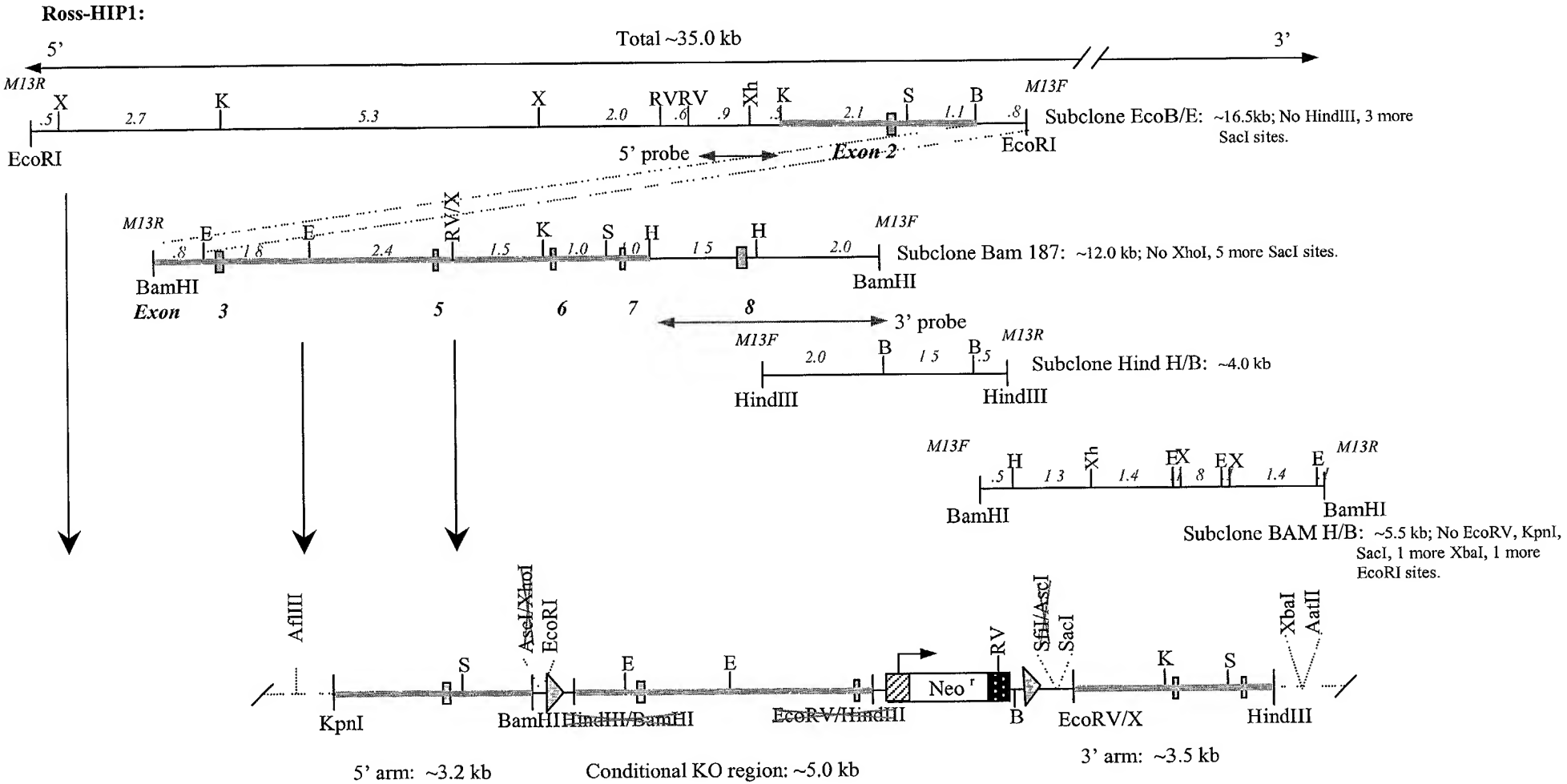


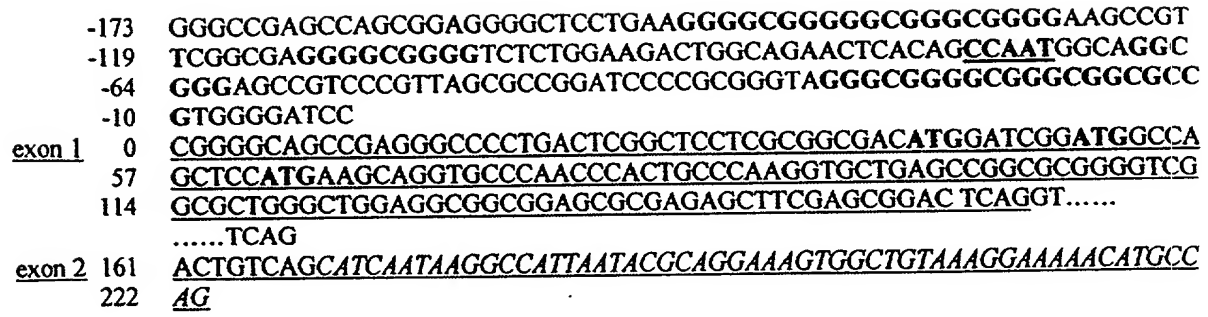
Figure 16

Vector Construction Strategy for conditional HIP1 knock-out



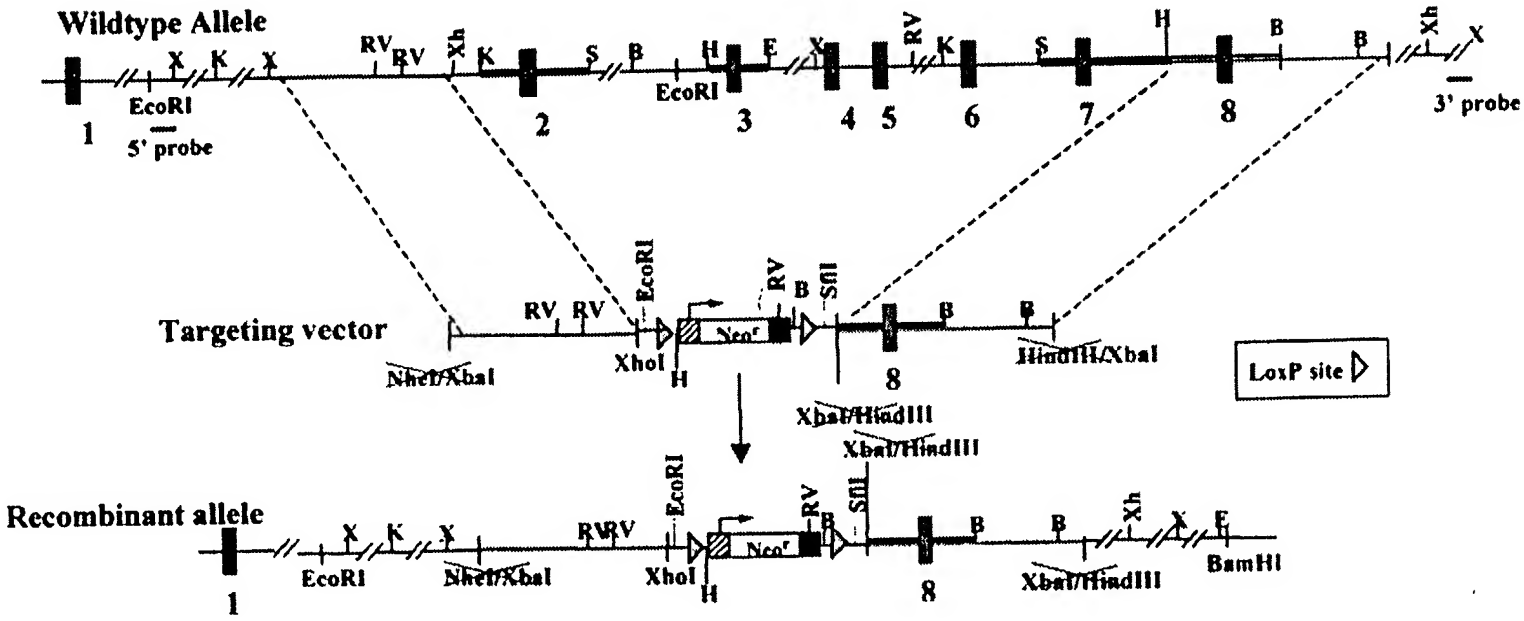
98TB/HIP1-con.
~15.5 kb

Figure 17



Redacted - 20/07/2005

Figure 18


Wildtype Allele
EcoRI
5' probe
3' probe
Targeting vector
NheI/XbaI
XhoI
LoxP site
XbaI/HindIII
Recombinant allele
BamHI

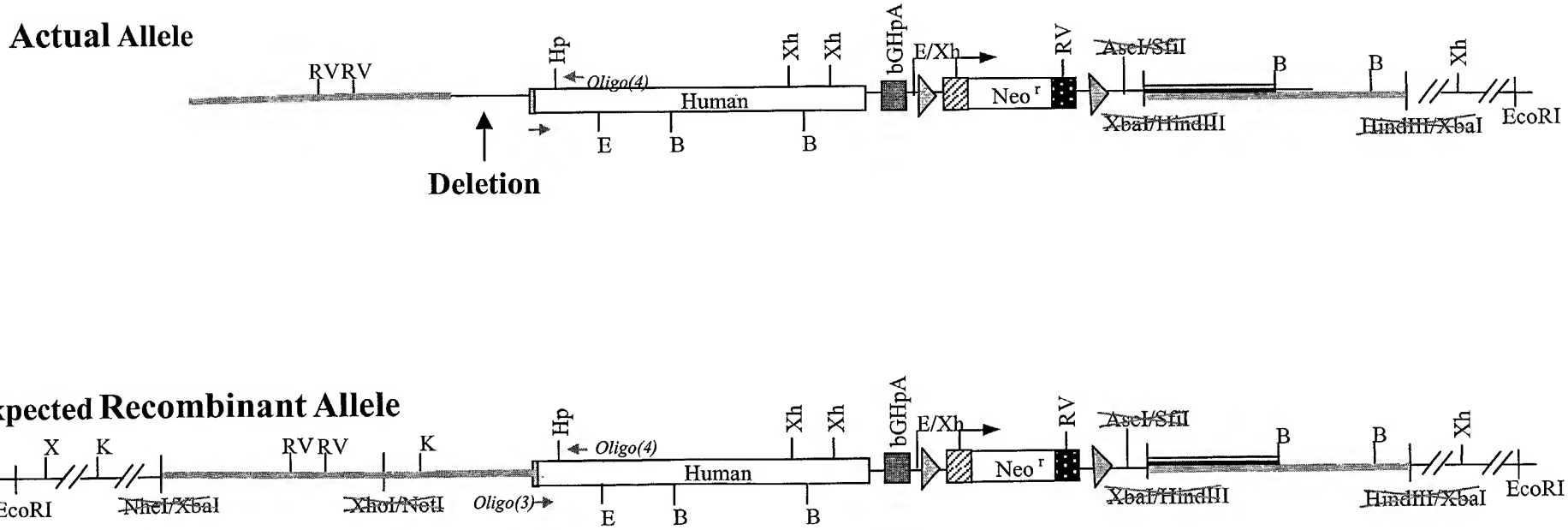



Figure 19
Deletion of the HIP1/PDGFβR knock-in ES cell allele